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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC SUBCOMMITTEE

OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

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Joseph Gootenberg, M.D.
Steven Hirschfeld, M.D., Ph.D.
Richard Pazdur, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. SANTANA: Good morning to everyone. I know that you all have very busy schedules and I do appreciate, and I am sure the FDA will appreciate, your being here this morning.

This is a meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee that has been called to seek the advice and guidance from all of you present here today with some issues in pediatric drug development that the FDA wants to consider both from a scientific and ethical point of view as they get requests from different sponsors in the future for new drugs and new biologics. I am sure Dr. Pazdur and Dr. Hirschfeld will expand on that.

What we will do this morning is we will have some brief introductory comments from Dr. Pazdur, then, we will have a conflict of interest statement, and then we will start with our meeting.

Dr. Pazdur.

Welcome

DR. PAZDUR: Thank you very much.

This is really the second meeting, I believe, of the Pediatric Subcommittee for

Oncologic Drugs Advisory Committee, and I would like to thank you all. This is somewhat of a diverse group since it has both adult medical oncologists and pediatric oncologists here, and I think reflects the issue that we are trying to address here, and that is the 1998 Pediatric Rule.

Basically, this mandates pediatric studies if the indication in an application under review can be found in children, so I think really we need an active dialogue between not only the pediatric oncology community, but also those of you who represent the adult medical oncology community.

Most of our applications come, not to develop pediatric drugs, but obviously to hit big tumor types, such as breast cancer, lung cancer, prostate cancer, and pediatric malignancies have somewhat been ignored in the development scheme.

We have really taken an interest since I arrived at the FDA to try to promote pediatric oncology both through looking at the Pediatric Rule again, but also various incentives that can occur for the pharmaceutical industry in developing drugs in pediatrics. So, this is really only one part of a more global picture of the FDA's interaction with the pediatric oncology community.

I am not going to spend a lot of time. I would just like to thank you for your participation here, and I think I will turn the table over to Steve.

Steve.

DR. HIRSCHFELD: I will in turn defer to Dr. Somers.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: This is the conflict of interest statement.

The following announcement addresses the issue of the conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Since the issues to be discussed by the subcommittee at this meeting will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products, in accordance with 18 U.S.C., Section 208(b), waivers have been granted to all members and consultants who have reported interests in any pharmaceutical companies.

A copy of these waiver statements may be

obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Irwin Bernstein, M.D., would like to disclose that he owns stock in Johnson & Johnson, Merck, Bristol-Myers Squibb, and Exelexis. Wyeth-Ayerst and the Genetics Institute provide research contracts to his employer, the Fred Hutchinson Cancer Research Center, for studies of an agent used to treat acute myeloid leukemia, and he is the principal investigator for the laboratory studies only of the agent. Dr. Bernstein is the inventor of the agent and is entitled to a share of any royalties that the center receives from Wyeth Ayerst. Dr. Bernstein is participating by telecon for part of this meeting.

Michael Borowitz, M.D., would like to disclose that Aventis supports some testing in his laboratory and a very small part of his salary.

Sharon Murphy, M.D., holds stock in Schering- Plough, Pfizer, Immunex, and ImClone

Equity holdings, Rhone-Poulenc Rorer, Pharmacia, Novartis, Sequus, and U.S. Bioscience provide financial support to the Pediatric Oncology Group, and Sanofi provides support to the Children's Memorial Hospital. Dr. Murphy is the past chair of the Pediatric Oncology Group. Further, Dr. Murphy receives consulting fees from Biogen.

David Poplack, M.D., previously received speaker's fees from Chiron and is an unpaid scientific advisor to Astra Corporation.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. SANTANA: For the record, we need to introduce ourselves, so I would ask, starting with Dr. Reynolds to my right, to speak into the microphone their name and their affiliation.

DR. REYNOLDS: Patrick Reynolds, Children's Hospital, Los Angeles.

DR. WEINER: Susan Weiner, Patient Advocate, the Children's Cause.

DR. SCHIFFER: Charles Schiffer, Karmanos Cancer Institute, Wayne State, in Detroit.

MS. ETTINGER: Alice Ettinger, St. Peter's University Hospital.

DR. BALIS: Frank Balis, Pediatric Oncology Branch, NCI.

DR. ARTHUR: Diane Arthur, Laboratory of Pathology, NCI.

DR. WAXMAN: Sam Waxman, Mount Sinai, New York.

DR. PITTALUGA: Stefania Pittaluga, NCI, Laboratory of Pathology.

DR. HEAD: I am David Head, Vanderbilt University Medical Center, Nashville.

DR. LINET: Martha Linet, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

DR. ARCECI: Bob Arceci, Pediatric Oncology, Johns Hopkins.

DR. HUTCHISON: Bob Hutchison, Hematopathology, Syracuse, Upstate University.

DR. SMITH: Malcolm Smith, Cancer Therapy Evaluation Program, NCI.

DR. POPLACK: David Poplack, Texas Children's Hospital.

DR. MURPHY: Sharon Murphy, Children's Memorial Hospital, Northwestern.

DR. PAZDUR: Richard Pazdur, FDA.

DR. HIRSCHFELD: Steven Hirschfeld, FDA.

DR. GOOTENBERG: Joe Gootenberg, Center for Biologics at the FDA.

DR. PRZEPIORKA: Donna Przepiorka, Baylor College of Medicine, Cell and Gene Therapy.

DR. BOYETT: James Boyett, St. Jude Children's Research Hospital.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the Committee, FDA.

DR. SANTANA: Victor Santana, St. Jude Children's Research Hospital.

Open Public Hearing

DR. SANTANA: The next item on the agenda is an open public hearing. Is there anybody in the audience that wishes to address the committee? If you wish to do so, there is a microphone in the middle of the room. Please stand up, state your name, and start your address.

Anybody in the audience?

[No response.]

DR. SANTANA: If there is nobody in the audience, we will go ahead and get started with the activities today.

The first presentation will be by Steven Hirschfeld from the FDA. Steve is going to try to define for us the charge of this committee from the FDA perspective.

Charge to the Committee

DR. HIRSCHFELD: Good morning. I want to thank everyone for coming this morning.

What I would like to do in just a few minutes is try to give the charge to the committee and attempt to focus the type of advice that we would be soliciting this morning.

[Slide.]

I will begin with a brief history of pediatric therapeutic development globally. Globally, pediatric therapeutic development has never been as thorough or robust as adult therapeutic development, and it is well documented that many therapies are administered to children without adequate study, and furthermore, many therapies are not made available for pediatric

study until after adult marketing studies are completed.

[Slide.]

The conventional pathway of therapeutic development is to begin with pre-clinical work and then develop an adult indication, and optionally, which is what the spaced dotted line represents, optionally, there may be some pediatric development, but this is not the only paradigm.

There are other possible paradigms where one may have pre-clinical development followed by concurrent adult and pediatric development, or never seen before in the history of approved pharmaceuticals, but there could be a model where one has pre-clinical development, pediatric development, and then optional adult development if it is warranted scientifically or economically.

[Slide.]

The FDA has attempted to address the issue of pediatric therapeutic development through some initiatives. In 1994, the FDA promulgated a Rule that established a principle of extrapolation for efficacy data from adult population to pediatric population if certain conditions were met. The Rule was intended to lower the barrier for studies

in pediatric therapeutics, but the results were disappointing.

In 1997, as a provision in the Food and Drug Administration Modernization Act, there was an incentive program for the development of pediatric therapeutics on a By Invitation Only basis, and while we will not discuss this at all this morning, I will mention that compliance with the 1998 Pediatric Rule, which we will discuss, can simultaneously be fused with compliance or an invitation to have an exclusivity extension, and there could be, in complying with the Rule, also a concurrent financial incentive.

[Slide.]

So, we will pause now on the 1998 Pediatric Rule. The 1998 Rule mandates pediatric studies if the indication for an application under review can be found in children. It applies to drugs and biologicals, and if the indication does not apply to children, then a waiver can be granted.

There is never an intent, nor should there be a circumstance, where development of a therapeutic for an adult population is in any way delayed or inhibited because of compliance with

pediatric priorities.

This circumstance is specifically addressed by the granting of a deferral for the submission of the pediatric data.

The 1998 Rule also does not specifically address the question of extrapolation of efficacy. The 1998 Rule raises the issue of are studies warranted, and that is the focus of what we would be discussing today in the setting of hematological malignancies.

So, the general question to the committee will be: How should the 1998 Rule be applied for hematological malignancies?

[Slide.]

Our goals, which we recognize may not be obtainable, and we recognize even if obtainable, may not be obtainable today, but our goals, nonetheless, would be to look for recommendations for adult indications that would trigger the Pediatric Rule, specific recommendations for adult indications that should be waived from compliance with the Pediatric Rule, and recommendations for general principles that may be used to apply the Pediatric Rule.

[Slide.]

What is intended by this concept of general principles? Well, one example might be a statement, such as if a lesion is necessary for establishing or maintaining the malignant phenotype, and if a therapy is directed against that lesion, then studies in tumors where the lesion occurs and has the same critical role are warranted.

With that, I close my presentation and look forward to what I hope will be an informative, interesting, stimulating discussion.

Thank you.

DR. SANTANA: Steve, I think we do have a few minutes, we are ahead of schedule, does anybody have any questions to Steve about the charge of the committee that he can directly address now? Go ahead.,

DR. SCHIFFER: Steve, maybe you can give us some examples of how this has been applied recently, for example, ATRA was studied simultaneously in adults and children. I mean how has this been done in a practical way?

DR. HIRSCHFELD: In a practical way, it actually hasn't come up specifically. We have looked at it. As an example, there was a recent

approval for arsenic trioxide for therapy, and we have applied some principles, and I will be explicit in how that was applied.

We wanted to look at defining the diagnosis on a molecular basis, so we defined the diagnosis, not on the basis of a French, American, British classification, but on a cytogenetic lesion. We wanted to define the place or the role of the therapy, not as something generic as first or second line, but specifically stated that it would be therapy which would follow a retinoid and an anthracycline therapy.

Then, when we asked how it would be applied to pediatrics, we noted that there were some pediatric patients that were included in the studies which we had encouraged and that there is a commitment to follow up with further pediatric data, and we do have data on file which establishes the pediatric dosing for patients who have that particular constellation of disease plus disease setting.

Does that answer your question, Dr. Schiffer?

DR. SCHIFFER: So, the label doesn't include pediatrics for ATRA and arsenic?

DR. HIRSCHFELD: ATRA, no; for arsenic, there is a statement, but it is not a robust pediatric indication per se. What we are interested in, and I should clarify this, is generating data, and as a byproduct of generating the data, we would be looking for labeling, but having labeling is not as important as having the studies done.

DR. HUTCHISON: Steven, a quick question which should help me understand this a little bit better, too, is what kinds of exceptions are implied by this ruling, and how is the term "warranted" interpreted, does that have teeth associated with it or does it not?

DR. HIRSCHFELD: Right. I think I can address that pretty clearly. The exceptions are for indications. An indication is a word that we are looking for some guidance in interpreting, but in indications which have up to now automatically generated waivers are colorectal cancer, breast cancer, non-small-cell lung cancer, prostate cancer, diseases which historically are not only not found in children, but we find that there is no linkage on a biological basis with pediatric diseases.

In terms of the teeth behind the 1998 Pediatric Rule, the redress is through the court system, and although this has never come up, if it should come up, then, the agency has the responsibility and the prerogative to bring an applicant to court and ask the court to either demand that the studies be done, which would be the first position, and the second position would be some other remedy which the court would determine. Now, since there are no legal precedents, we don't know what will happen.

Going back to how this has been followed up to now, to try to amplify on Dr. Schiffer's question, the answer is that we have been looking for a way to follow through, and we have not established a policy.

What we are trying to do through the series of meetings is evolve a policy through public discussion and consensus to guide us on what the circumstances or what the indications would be that would trigger the Pediatric Rule.

So, the compliance with the Pediatric Rule was not formal until December 2000, and until December 2000, even though the Pediatric Rule was published in December 1998, there was a time window

in which all applications could receive an automatic deferral, and that normally got us off the hook, but everyone else off the hook in that we didn't have to make a decision, but rather we could ask that the decision be deferred.

Time has come now to make some decisions, and we began the series of meetings in September 2000 in anticipation of having to comply with the mandate, and we have been seeking advice on the circumstances, and up until now, for better or worse, we have not had an application that has specifically addressed the 1998 Pediatric Rule.

DR. PAZDUR: I just wanted to clarify this because I think it is very important. When we apply the Pediatric Rule, this is a mandate, so the sponsor must do this, and I think that this is very important when you give us advice to have this consideration in mind.

We are requiring the sponsor to perform these studies, which is different, for example, from the pediatric incentive programs where we could say it would be nice if you did this, or please consider doing studies.

When the 1998 Rule is applied, it is a mandate, and as such, it may be questioned because

obviously, we are requiring people to do these studies, and therefore, once we start exerting some pressure on people or sponsors, there obviously could be this consideration of what are the indications really that can be extrapolated from the adult situation to pediatrics, how well founded is that in scientific data that would warrant an extrapolation of an indication, an adult indication to a pediatric indication.

So, it is a much different thing than it would be scientifically interesting to apply this Rule, it is a mandate, and therefore, that carries with it somewhat of a stick.

DR. SANTANA: Dr. Weiner.

DR. WEINER: Following up on what you said, Dr. Pazdur, I think that there is a very interesting contrast in language and one that I hope people would think about between the language in the example of your principle and the language in the example of the exclusivity provision.

The language in the exclusivity provision says studies that provide some benefit to children, and here it is a question of where the critical role is warranted.

I think that, you know, it is important to

place the principle in the context.

DR. SANTANA: Dr. Schiffer.

DR. SCHIFFER: So, if at the end of the day, Rick, we come up with a half dozen diseases that we think are similar biologically, and trials have been done in adults, like STI, for example, that means you would mandate trials in children because the diseases are similar or identical?

DR. PAZDUR: Potentially, we could, okay, and here again are we redefining how we define an indication and a disease, and I want to emphasize that this is a mandate as such, and therefore, I think we have to be quite explicit as far as the scientific robustness of the data that makes us make that recommendation, but potentially, that can be mandated.

DR. SCHIFFER: Does it go in the other direction?

DR. HIRSCHFELD: Yes. Dr. Schiffer, also, if we could have a list of diseases which should automatically be granted waivers.

DR. SCHIFFER: Occasionally, we learn from the pediatricians.

DR. SMITH: Steve, could you clarify the comment you made about ATRA, that there is no

pediatric section for ATRA, since there is clearly pediatric experience in children, in fact, were in the inner group ATRA trial?

DR. HIRSCHFELD: I will begin by stating that product labels often lag behind clinical usage, and all- trans-retinoic acid, trade name Vesanoid, although clinical usage is typically for front-line therapy for acute promyelocytic leukemia, it isn't specifically labeled in that regard, and the same with the pediatric information section.

That doesn't mean we are not interested, but the development of all-trans-retinoic acid, as well as most of the approximately other 80 drugs which are approved, and the other half dozen at least biologicals that are approved for cancer therapy, all had their evaluations and determinations made before the Pediatric Rule went into effect.

So, in part, it is to address, not only the absence of the pediatric information in labeling, but specifically to make the drugs or biologicals that are being developed available to investigators and available for study that we are looking to implement the Pediatric Rule.

Just as we often say studying the past is not a guide to the future, and that was just an example to show how there is a discontinuity between what is published, what is formally in the label, and what clinical usage is.

Does that answer your question?

DR. SMITH: Well, I mean yes and no. What is also published are the pediatric experience with ATRA, and so, I mean it is a drug that was studied in children and studied in a relatively timely manner in children, so it is then perhaps a situation where the studies were done, and children were able to have the advantage of receiving this agent, but somehow it didn't get into the label even though it made it into the published literature and other sources.

DR. HIRSCHFELD: Right. I would not use ATRA as an example of delayed development. I think Dr. Schiffer brought it up as just an example of a disease where one can make a linkage between the adult indication and the pediatric indication.

Now, to go back again to Dr. Schiffer's question, how has the Rule been applied to date, and I think the short answer is it really hasn't, that we are looking for a consistent and

predictable approach to apply the Rule.

DR. SANTANA: Malcolm, the way that I interpret it is if the sponsor was presenting ATRA today to the FDA for approval, and this committee says APL, or the group of experts says APL is really the same disease in children as it is in adults with many minor differences, and the sponsor wants to, today, obtain approval for ATRA, that the '98 Rule would mandate that those studies have to be done.

The problem is they can't go back because the Rule was not there yet. All they can do now, as I gather, is that they can then request for the exclusivity rule, that those studies be submitted to extend the indication.

Am I correct in that, Richard or Steve?

DR. HIRSCHFELD: Yes, I just would want to separate the words "exclusivity" and "rule." The exclusivity is a separate program which is optional.

DR. SMITH: The studies were done, though, it is not that the studies weren't done. They didn't make it into the label, but the studies were done.

DR. HIRSCHFELD: Right. Dr. Waxman.

DR. WAXMAN: The question I would have is when you mandate a pediatric study, does that mean that a drug would not be approved, if the diseases were similar in an adult and in a child, an applicant could not get that drug approved unless it was done in a children's group?

DR. HIRSCHFELD: Absolutely not.

DR. WAXMAN: What does it mean then?

DR. HIRSCHFELD: There is no linkage between the adult approval and doing the pediatric studies, and there would be no delay in the adult approval. The mandate comes from having the authority to ask, if need be, court enforcement of pediatric studies.

Dr. Head.

DR. HEAD: I have two questions, Steve.

The first is an operational one. Are the invited speakers participating in the decision or presenting data to a panel, and the panel makes the decision?

DR. HIRSCHFELD: Well, actually, there are no decisions that we expect to be made, so I would hope that everyone would feel comfortable saying whatever it was that they thought was important to say, and we will be reviewing the transcripts and

following up on a continuing basis with the people in this room and many others when it actually comes time to making decisions.

But what we wanted to do is set the framework and have it based on as sound scientific principles as the state of the science allows.

DR. PAZDUR: We are looking for recommendations and the scientific data to support those recommendations.

DR. HEAD: So, the speakers are here to recommend and provide data.

I have a second question. There are several levels that this can be considered at. The most simplistic level is, is the disease the same in pediatric patients and adults, but there are other considerations, is the host the same, and the hosts are different, are we supposed to consider that or not in our statements?

In other words, the effect of high-dose ara-C is much different in an elderly person, side effects, than in a young adult, or perhaps things affected in neurological development of infants, skeletal development, et cetera, and are we supposed to consider all of that or just consider the disease?

DR. HIRSCHFELD: All of the above.

DR. HEAD: To continue this, there may be different therapeutic goals in treating patients of different ages, so, for example, in myelodysplastic syndrome, in an elderly person, it is of great benefit to gain three to four years of life for that individual, whereas, in a child, the hope would be to cure the disease, so quite different goals even though the disease may be very similar.

Is that also a consideration?

DR. HIRSCHFELD: It is a consideration, and I think all the issues, all the points you raise are points which we had hoped to discuss during the course of the day, and then whatever is discussed here would not again be a final determination, but rather just a series of issues and recommendations to follow through with, and the more explicit the recommendations, the more helpful the discussion would be.

DR. PRZEPIORKA: A question about the term "studies." Clearly, there may be no financial incentive to fully develop a drug for a pediatric use, and so I wanted to ask when we think about what the diseases that we recommend you mandate studies in pediatric patients, what degree of

studies will this be, just pharmacologic studies or all the way to Phase III randomized studies?

DR. HIRSCHFELD: Excellent question, and that foreshadows a meeting which we have planned later this year, and we have what we hope is a logical end-stage process in that we will first discuss the nature of the indications, and once we have some focus and some consensus on which indications, then, we will be having a meeting we hope in September of this year, but the date hasn't been established, where we will discuss the types and formats of studies.

In some instances, it may be just doing some pharmacokinetics and perhaps some pharmacodynamics, perhaps it will be an issue where one knows enough about the diseases and is comfortable enough with how they are similar, that one could have a combined trial, and in other circumstances, it may require a proof of concept study, but the format of the studies is not something which we will discuss today or decide on, but we have in the back of our minds that it is an important question to address.

DR. ARCECI: I hope it is appropriate to just ask Susan to clarify your comments on benefit

versus exclusivity, that you were talking about, because it seemed important and right to the point, but I wasn't quite sure exactly where you were going with that.

DR. WEINER: I just meant to comment on the contrasting language between the statute and the term "warranted," as Steve has given this example today. The focus in the congressional language was clearly on the studies that would benefit children, whereas, here, the relationship is several steps away.

I would just hope that somehow or another that when the studies are discussed and the recommendations come through, that that emphasis is pervasive, that is, that the emphasis on kids and what is going to benefit kids is pervasive.

DR. ARCECI: Thank you.

DR. HIRSCHFELD: If there are no further questions, I will turn it over to Dr. Santana.

DR. SANTANA: Thanks, Steve, for all those clarifications. I knew they were coming, so I am glad we did it.

We are going to go ahead and start with the presentations. Dave Poplack will start us off with the Challenges and Considerations in Linking

Adult and Pediatric Leukemias.

David.

Challenges and Considerations in Linking Adult and Pediatric Leukemias

David Poplack, M.D.

DR. POPLACK: Thanks very much. I want to compliment Dr. Pazdur and Steven for putting pediatric oncology on the FDA's radar screen and for having this meeting.

[Slide.]

What we have been really asked to do by Steven is to explore the relationship between pediatric and adult leukemias, and more specifically, determine areas in which there may be compelling biological evidence of similarities or differences that are useful in guiding the drug development process.

[Slide.]

Another way to phrase this is that we are being asked to respond to the question as to whether there are defined subsets of adult and pediatric leukemias that share biologically relevant features that might mandate that they be commonly studied.

[Slide.]

What I will try and do very briefly as the first speaker is to give you a brief overview of the situation in terms of adult and pediatric leukemias and to discuss some of the promise and perhaps rationale for asking this question, but yet also to highlight some of the challenges that we might have in trying to address it.

[Slide.]

This slide simply illustrates the distribution of adult and pediatric leukemias and provides information that I am sure most of you are aware about, which indicates that, for example, acute lymphocytic leukemia is more common in children than in adults, and that acute myelogenous leukemia is more frequently seen in adults than in children.

One of the points that Steven mentioned was that we should also suggest situations in which it may be superfluous or inappropriate to consider that simultaneous studies be done. Certainly, since chronic lymphocytic leukemia is not on the radar screen of pediatric oncologists, and chronic myelogenous leukemia, at least the adult form, is extremely rare, those might be considered situations that would not be appropriate for the

type of discussion we are having today.

[Slide.]

I think we are all, and you are all, aware of the fact that adults have a worse prognosis.

[Slide.]

This slide simply illustrates the survival of adults and children with the two most prominent forms of acute leukemia, and shows you that in both circumstances, children do do better, and the reasons for this, of course, aren't clearly understood. They may have to do with differences in biology, with pharmacokinetics and pharmacodynamics, clearly with host status, as David Head had suggested, all of these have to be considered.

[Slide.]

I think one of the things that we have learned over the last 25 to 30 years in particular is that it is no longer really appropriate to consider the acute leukemias as two separate entities, acute myelogenous and acute lymphocytic, and to lump them together under those headings, because, in fact, these are really a heterogeneous group of diseases.

[Slide.]

I would like to illustrate that just through the example of childhood acute lymphoblastic leukemia. This slide simply illustrates data from the Children's Cancer Group showing the dramatic improvement overall in survival that has occurred in the last 35 to 40 years in treating childhood acute lymphoblastic leukemia.

Each of these curves represents a different clinical protocol. We have made tremendous strides, as you can see. In fact, it is considered one of the true success stories in modern medicine.

In part, in particular of late, one of the reasons for these successes has been because we have appreciated the fact that acute lymphoblastic leukemia is, in fact, a heterogeneous group of diseases and there are biological differences with the disorders that are lumped under that category.

[Slide.]

The evidence for this comes from a variety of studies and a very large literature in a number of fields, that started with the recognition clinically that patients present in different ways and that one could, when one went back

retrospectively looking at these types of studies, define certain features evident at the time of diagnosis whether it is the initial white count or patient age, a variety of features that were linked to prognosis.

Of course, the attempts to classify the disease on the basis of morphology, cytochemistry, immunophenotyping, and there the approaches have become highly sophisticated, and more recently, using cytogenetics and molecular phenotyping, have all just provided increasing evidence that this is really a group of diseases that are distinctly different in terms of their biologies.

[Slide.]

What has been the impact of understanding and appreciating this heterogeneity, well, clearly, it has had an impact on therapy in the following way - is that understanding that one can define risk groups for prognosis has allowed investigators to stage patients according to the degree of risk and to actually develop or tailor therapy accordingly, such that low risk patients over recent years have been treated with effective therapies, but less toxic in nature, and high risk patients, those presumed to be at a high risk of

relapse, have been treated with more intensive treatment, and generally, this has been a successful strategy, but I want to point out that many of the initial prognostic criteria that were identified by looking back and developing statistical associations, for example, between prognosis and initial white count, et cetera, provided clues, but really little in terms of biological insights into why they were good or poor prognostic factors.

[Slide.]

Clearly, however, things are changing and there is no question that now, and as we go forward in terms of technological advances, we have at hand tools which will allow us to really work within a new paradigm where we have tools that are going to allow us to develop more biologically relevant bases for classifying these disorders both in pediatrics and in adults, and also to allow us to identify molecular targets for therapy.

I think it is important to recognize that this discussion of differences and similarities between adult and pediatric leukemias is occurring on a constantly evolving technological stage.

[Slide.]

Just, for example, in the area of cytogenetics, we have made quantum leaps in our ability to define the chromosomal aberrations that occur in these disorders, and this slide simply lists a whole host of different technologies that allow us, with greater refinement, to determine that there are indeed chromosomal aberrations and to define them, and to even go farther in terms of identifying with molecular techniques what is actually happening, for example, at the site of a translocation.

[Slide.]

This slide simply illustrates, for those of you not familiar with it, the technology of spectral karyotyping, which in a very highly sophisticated system which involves computerization, individual chromosomes are painted, and one can determine with much greater resolution the presence of translocations.

Here, you can see a 12-15 translocation in ways that could never be identified previously, so we are able to look at the karyotype in a much more complex and sophisticated way.

[Slide.]

Then, naturally, in the area of molecular

biology, we now have at hand tools which will allow us to genotype and phenotype and again increasingly sophisticated manners. We have gone beyond in a sense Southern and Northern and Western Blotting, and PCR technology is at hand, but there is tremendous promise in the concept of using cDNA microarray to determine differential gene expression and the other technologies listed on the slide, hold great promise.

So, I think we need to recognize and appreciate, as I am sure we all do, that in the future, we are going to better be able to define similarities and differences. Things are really moving quite rapidly in this area.

[Slide.]

This slide simply illustrates panels taken from a microarray, analysis of gene expression in patients with two forms of leukemia, showing differences in gene expression.

[Slide.]

This data from a study done by Dr. Judith Margolin in our institution in which she compared the gene expression using microarray of the t(4;11) translocation to pre-B ALL shows that there are different genes expressed.

[Slide.]

For example, here, in the t(4;11) circumstance versus CALLA-positive pre-B ALL.

So these technologies are at hand, and they need to be studied prospectively in both children and in adults.

[Slide.]

Given the fact that we are working with a changing playing field, can one at the present time define at least theoretically subsets of adult and pediatric leukemias that might be appropriate for common therapeutic studies?

I would submit that, in fact, yes, we are able to define certain areas.

[Slide.]

For example, in the acute lymphoblastic leukemia category, we are aware, using cytogenetics, and these next slides are going to focus on cytogenetics in particular, entities that are clearly shared between pediatric and adult lymphoblastic leukemia.

The Philadelphia chromosomal translocation BCR-ABL translation that has been mentioned already, is clearly one of those circumstance. Patients with a t(4;11) translocation and other

11q23 abnormalities. B-cell disease characterized by a similar translocation. All of those are associated with relatively poor prognoses.

At the bottom of this slide, you see the TEL-AML translocation situation, one which is perceived to be associated with a better prognosis, but even though we may not have the biological information that goes along with the observation that a higher or lower than normal chromosomal number may be associated as in the case of hypodiploidy with a poor prognosis, or hyperdiploidy with a good prognosis, these differences do exist in pediatrics and childhood, ALL, and may be the basis for studies in the future.

[Slide.]

In terms of myeloid leukemia, again, the situation of the t(15;17) abnormality and other APL variants is one that has already been studied and would be appropriate to be studied in both circumstances, as would the t(8;21) translocation even though, "it is associated with a better prognosis," in fact, we are really doing quite poorly with this disease, and it may be appropriate to do a combined study.

Then, I would submit that therapy-associated myeloid disease might be an appropriate focal point for combined studies because we are seeing both in pediatric and in the adult community increasing numbers of patients with this disorder.

[Slide.]

Of course, now we are in a new era of molecular targeting and perhaps two examples here are really worth noting, and they have already been mentioned, and that is, that we have already been able to demonstrate that one can target therapy specifically for abnormalities present at these types of translocations, in the case of the STI 571 study occurring in patients with the BCR-ABL translocation, and in the use of ATRA, for example, to treat patients with a t(15;17).

I think these experiences really are sort of poster children for the concept of targeted therapy, and they provide compelling arguments, I would submit, first of all, in terms of confirming the validity of targeting relevant molecular lesions and also providing a supportive argument for testing targeted agents in all relevant populations.

[Slide.]

One of the challenges that Steven asked us to respond to is whether we could actually develop a general principle that might guide the identification of biological subsets that would be suitable for study both in adults and children.

[Slide.]

As Dr. Hirschfeld did, I believe that any characteristics that are defined have to be associated with lesions that are linked to either the establishment or development or the maintenance or progression of the malignant phenotype or perhaps linked to the development of resistance to specific treatments for these disorders. But this will be a subject I think of discussion over the day.

[Slide.]

I didn't want to leave you with the impression that it starts and ends with cytogenetics. There are clearly examples of a whole host of biological features that may be shared by adult and pediatric leukemias that may be worthy points of discrimination between the two, and worthy candidates for combined study.

They are listed on this slide, but

One need only look at the BCR-ABL situation in which there have been at least two different distinct fusion proteins identified, which may, in fact, be associated with different downstream events.

We know that in childhood ALL, with the BCR-ABL translocation, that there is a different fusion protein than seen in the majority of adults, and so it may be presumptive for us to believe that a therapy identified or targeted specifically for the translocation may have similar therapeutic results in both populations.

Also, I would offer as another example the t(1;19) translocation where the translocation may be present, but there have been differences noted and observed in expression, which may be associated with different prognosis. So, one can't be too simplistic and simply say because there is a translocation, and if we can target it, or the downstream events, that we are going to have similar results in adult or pediatric populations.

One also has to remember that these lesions usually occur in the context of other genetic changes that are occurring in these diseases, such as concomitant aneuploidy, which may

have significant impact on the biological expression of these translocations, so we have to be careful.

[Slide.]

The other issue was raised again by David Head, which has to do with host tolerance and differences that relate to toxicities. When one deals with children, we are dealing with developing tissues, with developing neural tissue, for example, and with a growing organism, and in contrast, the situation is quite different in dealing with the fragilities of individuals at the older age of the spectrum.

We know already that there are agents that are used even now to treat, for example, acute lymphoblastic leukemia both in adults and in children that have at least widely different clinical impressions of toxicity, and I will offer asparaginase as a perfect example of a drug that appears to be much better tolerated in children than in adults, and where now that aggressive use of asparaginase has become a fairly common theme in childhood leukemias, there has been some resistance to try and apply that in adult ALL because of the fact that adults appear to have greater toxicity.

So, we always have to be cognizant of the possible issues that relate to toxicity. Perhaps the major problem, however, is small patient numbers, and it wonderful in theory to define these subgroups, but if you then say, well, how do I really develop a trial, even in BCR-ABL translocation, by my calculations, there probably are only 150 to 200 children in the country who have this type of abnormality.

Most of these translocations occur in 5 percent or less pediatric patients with ALL, for example, and so therefore, it is going to be extremely difficult for us to develop studies in which we are going to be able to get sufficient numbers, and as the prognosis and as our therapies get better for those different subsets, the studies paradoxically are going to require greater numbers of patients to show validity, so it is not going to be an easy process by any means.

Another point, I think, is that many of these subsets are already being, if you will, taken out of the study pool by other available therapies, such as transplantation, and where, for example, therapy-related secondary myeloid leukemias in most centers or in many centers are being automatically

given bone marrow transplants, and that may be an appropriate therapy, and I am not comment on it, but many of these subgroups may already be defined for different types of therapy, making it more difficult for us to apply new approaches to this subset.

[Slide.]

So, are there benefits to attempting to design and implement common adult and pediatric leukemia trials? Clearly, I think so and obviously, the ultimate benefit would be new and improve therapies for our patients. Clearly, that has to be, as Susan Weiner pointed out, the factor that motivates all of us.

Clearly, by doing this, I think we will arrive at a better understanding of the underlying biology of these diseases, but as I pointed out, it is not necessarily going to be easy.

[Slide.]

I would like to make a plea for the development even now--and it is wonderful to see pediatric and adult leukemia and lymphoma specialists and experts in the same room, I think we need to do more of this--and I think what we need to start to do at this point is to develop

common, comprehensive prospective biological studies of these diseases.

Hopefully, that can be commonly coordinated using these new and advanced technologies, so that we don't miss the opportunity to be able to use the new technological advances to define with greater certainty biological subsets in the future.

I would also like to point out that it is important to study, I believe, both the good and the poor prognostic groups. It is natural and appropriate for us, and certainly from an economic point of view, to focus on where the need is. We need to learn what is going on with patients who have, for example, a bad translocation, but we also, and particularly I think of the promise of cDNA microarray in gene expression studies, need to learn what has happened in patients who have done well on the therapies that we have, and can we come up with information gleaned from evaluation of those patients using these new technologies that may be relevant and appropriate for us to utilize or give us clues to, treatments that could be utilized in the poor risk groups.

[Slide.]

So, in summary, I think even now it is probably possible for us to identify classification techniques in adult and pediatric leukemias that can identify subsets in which joint treatment protocols are justified, but no question that significant caveats to the strategy exist.

Again, I would make a plea for the development of coordinated prospective biological and clinical studies of adult and pediatric leukemias, using the latest genomic technologies. I would also suggest that there may be value perhaps stimulated by this meeting here done at the behest of the FDA, and perhaps coordinated either by the FDA or the NCI for the development of a working group or a forum that might begin to take a hard look together at adult and pediatric leukemias and lymphomas, because I think we can only benefit from pooling our knowledge. For too long we have really sort of done and developed therapies in our own spheres of interest, and I think it is very important to share information.

I think I will stop here and thank you very much.

DR. SANTANA: Thank you, David. I think you have set the stage for some point that we will

catch up in the discussion period, and we will try to answer those questions then.

I am going to go ahead and invite Dr. Murphy to do her presentation as it relates to adult and pediatric lymphomas.

Sharon.

Challenges and Considerations in Linking Adult and Pediatric Lymphomas

Sharon B. Murphy, M.D.

DR. MURPHY: Well, Dr. Hirschfeld assigned me the task of describing the potential advantages or pitfalls of linking adult and pediatric lymphomas. Along with Dr. Poplack, he asked that we provide a global introduction, an overview, if you will, of the advantages and disadvantages of, if you will, lumping versus splitting, and try to identify some principles for defining which criteria for which lymphomas could be considered essentially the same or different in adults and children for the purposes of applying the Pediatric Rule.

I must say that we were encouraged to talk to each other before this session to harmonize our global introductions. That opportunity did not arise, but it is nonetheless interesting. You will

hear some themes that we both independently identified, I think.

Before jumping into lymphoma classification, which I know you are all anxious to do, I want to first give some of my personal perspective about the issues this Pediatric Subcommittee of ODAC is struggling with in applying these new regulatory initiatives which are, after all, aimed at producing health benefits in children.

Now, I also want to confess--this is like a disclaimer or a disclosure--that I have really been struggling with some very fundamental problems in applying this Rule and preparing this talk that I just find very difficult to reconcile.

So, upfront, I would like to say that, on the one hand, for my whole professional life as a pediatric oncologist, I have been preaching the mantra, you know, children are not just small adults, and furthermore, that pediatric cancer is very different than adult cancer. We have all said this a million times.

But from the standpoint of the Pediatric Rule, it makes sense perhaps to say that, well, the diseases are really the same, not different, so

that we can get drugs early on the market with pediatric information as a mandate.

So, it is clear to me that since the legislation has been enacted, there actually has been a huge increase in pediatric studies for new drugs and for drugs already on the market, drugs that are really quite important to treat pain, asthma, hypertension, seizures, infectious processes, but that the hope for stimulation really of research in pediatric anti-cancer drugs has not materialized whatsoever as we all know, and that is why we are here today, to provide some advice to the FDA, which might help to shape maybe a more flexible interpretation or a liberal application of the Rule or something in order to better realize the original intent of the law, which is to provide more health benefits for children, have incentives for the pharmaceutical industry to conduct these new drug studies, so that children with cancer could benefit from the knowledge gained and have greater access to new treatments. That is what we all want.

So, I just want to clarify if we say today that pediatric cancer in general, or leukemias and lymphomas in particular, are different from the

diseases in adults, then, the Rules will not apply, and a full or a partial waiver would be extended to the sponsor relieving them of the requirement for these pediatric trials, and that is sort of a politically incorrect outcome for children. So, we have to be careful of what we say today, but at the same time we have to say what we know to be true based on the evidence and also all of our collective knowledge. So, I have quite struggled with this conundrum.

If I can be allowed to make a few more comments of a general nature, I would like to do that, because a lot of people will talk about lymphomas, I am sure.

[Slide.]

The advantages obviously of this pediatric provision are to stimulate the development of new therapeutics for pediatric indications, the whole point being to produce public health benefits for children in return for which an exclusivity extension may be granted, which is a financial incentive that has attracted much interest in the pharmaceutical industry.

We have representatives from the pharmaceutical industry here in the audience today,

and I hope that they will chime in, in the discussion period.

There is also at the bottom here, and I put a question mark, the theoretical advantage of having early access to new agents for children. As I said, at least in cancer, this has not materialized because I think that the prospect of six more months of additional exclusivity for a company, for a product, that has yet to be approved, and when it is approved, will enjoy up to 15 years or more of freedom from generic competition, it is just not compelling to them, and it just doesn't seem to outweigh the risk I think that industry perceives, that if you let the drugs out early for children, there may be adverse events or adverse experiences that might jeopardize their approval, and the hoped-for widespread application for adult indications, so this has not worked, and there has not been early access to new agents as a result of this legislation.

[Slide.]

This next slide is some of the pitfalls and harms of this--potential, these are potential pitfalls, it hasn't really been applied yet, so it is all hypothetical--one problem alluded to by

David is the limitation of adequate patients eligible for Phase I/II early trials of pharmacokinetics and pharmacodynamics or for the, if need be, Phase III pivotal trials.

This is particularly true in pediatric cancer where, as we well know, the success of our front-line therapies, especially in leukemias and lymphomas, markedly reduces the number of children who have recurrent or refractory disease who might even be eligible as candidates for Phase I or II studies of new drugs.

The numbers actually become even more limiting, and you will see this later in my slides. When we consider the distribution of different kinds of NHL, because just as NHL is not one disease, it is the same problem as in leukemia, there is lots of different kinds of lymphomas, and when you start slicing up these different kinds, and looking at the numbers, you really get into almost infeasible situations of ever conducting trials.

I have also listed here under the issue of ethics, the significant problem of protection of vulnerable child subjects of research, and the dubious ethics of the reality or even the

perception of profiting from industry-driven studies performed in children.

Already, in the New York Times and other places, strong concerns have been raised that only blockbuster drugs, like Prozac and Claritin, are being studied, resulting in frankly billions of dollars of additional profits from market exclusivity from the manufacturers. This tends to leave the rarer illnesses and diseases left out, like leukemias and lymphomas and anti-cancer things.

So, I just caution we have to be constantly aware of that problem.

Lastly, I have put the information down that might come up in the discussion, that hasn't yet, and that is, that from the Pediatric Rule, orphan drugs are excluded. We know pediatric cancer, particularly it is not one disease, but many different kinds of disorders, and actually, each one is kind of an orphan disease if you think about it.

Wilms' tumor affects 500 or fewer children per year in the United States. In the case of a common malignancy, like ALL, there is a few thousand kids annually, but of the various

different kinds of lymphomas, there is only hundreds or tens of tens affected if we split them down to different kinds, and orphan drugs don't fall under this, but really a lot of adult leukemias and lymphomas are orphan diseases, too, you know, like hairy cell leukemia or certain rarer types of hematologic malignancies seen in adults don't affect lots of people either, so how we are going to do this is a very challenging thing.

Now, I have just a couple more general slides and then I will get to lymphomas, my assignment, but I thought I would just now focus on pediatric cancer and the pitfalls of applying this provision.

[Slide.]

The first is the differences between pediatric cancer and other diseases of childhood, like infectious diseases or asthma or epilepsy, which may fit easier in the Pediatric Rule than does cancer, which is not one disease.

Then, of course, we have the well-known differences between pediatric and adult cancers, and most important for today's discussion, I think, is a big pitfall, is the lack of validation or evidence of the relevance of the models being

proposed to apply the Rule, which we have talked about before, in the previous meeting and Steve's introduction, things like specific mechanisms, pathways, gene expression, profiling, all of these proposed models which might be applicable or designed to apply the Rule have not actually been validated in a strict way, so there will be limits in applying them. Let's not forget that.

This brings me back to why we are here today, which is to ask the question is it justified--or why I am here today--is it justified or not to link adult and pediatric lymphomas.

[Slide.]

I am going to start with lymphoma classification, this being my favorite simplification, as much as I am going to get into classification.

There is Hodgkin's disease and there is everything that is not Hodgkin's disease. Of the non-Hodgkin's lymphomas, we have the B-cell derived, T-cell, and NK-cell derived tumors.

If we ask ourselves whether, for the purposes of the Pediatric Rule application, lymphomas are the same in adults or in children or different, I would state that Hodgkin's disease is

the same, but that non-Hodgkin's lymphomas are mostly different, unless we use the really simplistic argument that lymphomas in adults and children must be the same because they are all derived from lymphoid cells. No, I don't think so, but there is one way to group them.

They are all derived from cells of the lymphoid system. Now, I expect most people to be in general agreement with my statement that Hodgkin's disease is the same, so I really want to spend the rest of my time discussing non-Hodgkin's lymphoma, and I want to approach this discussion from a developmental perspective, if I may. It is the paradigm I am going to use for my remarks, and I will focus on the cells of origin, first, of B cells, then of T cells, and then give an overview.

Now, this is where I have to switch media, if I may. I have some old-style slides that are not on PowerPoint.

[Slide.]

This is actually a lovely slide I have taken from Ian McGrath's publications, which I greatly admire, and this is a schema that he has proposed of B-cell differentiation, the vertical pathway being primary differentiation, which is

antigen independent, and the horizontal being so-called secondary differentiation, which is antigen dependent and takes place inside the follicular center of the germinal centers.

Now, on one side of each of the putative cells, you see the markers, and on the other side, you see the counterpart transformed neoplastic lymphoid cancer that might be derived from that normal counterpart, frozen at that point in differentiation.

So, what you can see, for instance, starting at the top here with some multi-potential lymphoid cell early in differentiation, antigen independent, proceeding along B cell differentiation pre-B, then development of surface immunoglobulin, expression from immunoglobulin gene rearrangements, you see that the counterpart cells are the kinds of things we see in pediatrics, pre-B cell, B precursor ALL, et cetera.

In contrast, this part of secondary differentiation inside follicular center cells, where you have centroblasts, immunoblasts, differentiating to plasma cells or small memory lymphocytes, these are the phases of differentiation from which the counterpart

neoplastic cell is the kind of lymphoma we see among adults, follicular center cells, myeloma, et cetera, so keep that in mind.

[Slide.]

Now, switching to the next slide, which is T-cell differentiation, think of this as a box with the box over here being the thymus. Again, on one side the normal T-cell, the cortical thymocyte or early thymic precursor, the stem cells, and then outside the box is the post-thymic peripheral T cells.

The counterpart cells again in lineage terms, the earlier cells in the thymus and early phases of T-cell differentiation are the ones we see that produce lymphoblastic lymphomas and leukemias in children.

The post-thymic, so-called peripheral T cells, like Sezary, mycosis fungoides, CLL, these are the more adult type putting it in a developmental perspective.

[Slide.]

This is another paradigm here if you accept this notion I have put forward, and you look at life as the continuum on the age spectrum. You look here at life starting from childhood to

adults, and you look at lymphoid malignancies and their relative frequency, I think it is fair to say that in early childhood and adolescence, the relative frequency of cases of lymphoid malignancies, lymphomas and leukemias, is from precursor cells, and later in life, it is from the mature cells.

This is also true, I might point out, of other forms of pediatric cancer, which mostly early in life are derived from embryonal cells early in development, neuroblasts, retinoblasts, rhabdomyoblasts, you name it, they are nephroblasts.

These are really developmentally conditioned tumors in contrast to the more common tumors of fully differentiated mature epithelial tissues that are common in adults, breast, colon, prostate, and lung, and we know, for instance, this is the majority of adult cancer and only 4 percent of pediatric cancers or carcinomas. So, we have this developmental difference.

[Slide.]

Now, why in lymphomas and leukemias do we see this? Well, the obvious observation again is that the cells of origin in children are, if not

actually stem cells, at least they are in proximity to lymphoid stem cells, I think, so the hypothesis, not only mine certainly, but supported by the evidence, would be that childhood lymphomas are the result of somatic mutations occurring at a particular point in time of maximum cellular proliferation, differentiation, and clonal expansion.

That is a hypothesis supported by some of the genetic evidence where you see these common, non-random, recurring chromosomal abnormalities that characterize pediatric lymphomas and leukemias, and the affected genes at the breakpoints with those loci, which primarily are, for the lymphoblastic lymphomas, T-cell receptor genes juxtaposed to other master genes or transcriptional regulators.

Small, non-cleaved cell lymphoma, B-cell Burkitt type we know. We have the immunoglobulin loci, and here we have the only other non-random loci in large cell.

So, I think it is fair to say that particularly these non-random chromosomal abnormalities are mostly entirely different from the kinds of chromosome changes you see in adult

lymphomas, I think there would be little argument about that. Where the common genes involved are genes like BCL-1 BCL-2, BCL-6, regulating not T-cell receptors or immunoglobulin gene rearrangements, but regulating things like apoptosis and cell cycle control, which are much more common in follicular center cell biology. So, that is a bit of a developmental argument for how they are mostly different.

Now, if I may, I would like to stop the slides and go back to just the last few other points here, developmental paradigm for lymphomas. I want to finish up with some other evidence that relates to this developmental paradigm and the differences in the cell of origin and show how that is reflected in the differences in distribution of the types of lymphomas that are common in adults and children.

You probably all know this, and I am certain we will have more discussion of it later, but I thought I would hit a few high points.

[Slide.]

Now, on this slide, I have listed the relative incidence of the more common types of lymphomas observed in children and in adults.

In pediatric lymphomas, basically, they are all high grade and about 30 percent or so are lymphoblastic, close to 40 are Burkitt small, non-cleaved, and about a third are large cell. There is 1 or 2 percent in there that may be other or nodular, but that's it. We have these three kinds of lymphomas in pediatrics for practical purposes.

The types of lymphomas prevalent among adults are listed here, taken from the very large International Lymphoma Study Group Classification Project that I have listed the references down here, and you can see that almost 50 percent or nearly 50 percent are B-cell derived, diffuse large cell being the most common, and 22 percent are nodular or follicular. This is in pretty much the Western World, different in other parts of the world, but let's leave that out.

There is 6 or 7 percent of marginal zone, multi-peripheral T cell, small lymphocytic lymphomas, the tissue equivalent of CLL, and about 6 percent mantle cell. You can see that there are fewer than 2 percent, 1 or 2 percent of adult lymphomas with either Burkitt's or precursor T-lymphoblastic, which are the most common, and 18

to 20 percent of lymphomas in adults are other kinds not listed here meaning they are rare in adults, too.

Let me not show any more slides and in the interest of time, just propose a conundrum that I have tried to think about, how would we apply this Rule.

I wanted to pick an example of an important new biologic active in adults with B-cell lymphomas, and that is rituximab anti-CD20, which I am sure you all know is approved for use for treatment of indolent lymphomas in adults.

I am asking myself would it be appropriate even to hypothetically mandate studies of this new agent in children if it were to come up now for a rule, and particularly I am not aware of any good pediatric trials done to date with this compound. There is only anecdotal use of rituximab in children.

Now, if you recall, monoclonal antibody therapy for lymphomas was really pioneered by investigators at Stanford, who actually began their biologic treatments of lymphomas with anti-ideotype antibodies, which are patient specific and, of course, more cumbersome and difficult to produce,

so it was natural for them to want to try an antibody, a monoclonal antibody that had a broader specificity, wouldn't have to be manufactured for every patient, and so the notion of directing an antibody to some surface antigen like anti-CD20 was a natural one.

It was logical also to test that approach first in adults with follicular lymphomas, which has a natural history of being very indolent, of relapsing, recurring, going on for years, giving you lots of time to assess responses, and the disease proceeds at a leisurely pace. In many settings, it is even a watch and wait for those kinds of patients.

So, how would you do rituximab studies in children or how would you even apply a principle for the mandate to apply, because CD20 is a differentiation antigen, it is not necessary for either establishment of the disease or maintenance of the malignant phenotype certainly, using the Rule proposed, and would we have to mandate studies of anti-CD20 for any lymphoid malignancy expressing CD20? How strong would the expression have to be?

I am sure Dr. Borowitz will enlighten us and clarify the point that it is more strongly

expressed in adults with follicular lymphomas than in the high-grade B-cell Burkitt type that we see in children, but for the life of me, I can't figure out what kind of principle you would apply, and this is a very important new biologic for treatment of lymphomas, and I just came up stuck with that.

So, I think I will close and we could have some discussion on how all of this might apply.

Thank you very much.

Discussion

DR. SANTANA: Thanks, Sharon.

Well, we have had two very challenging presentations and I want to go ahead and open up the discussion.

Anybody on the table who wants to specifically address issues or questions with David or Sharon? Donna.

DR. PRZEPIORKA: Two questions for Dr. Poplack, one leading to the other essentially.

You showed a very nice slide, I think the third to the last or second to the last slide, comparing outcome of various types of ALLs between pediatric and adult patients. Just to follow up on that theme, I know there are not very many pediatric patients with adult type CML, but the

prognosis for adult type CML in pediatric patients compared to adults?

DR. POPLACK: They do reasonably well actually, the adolescent patients, but heretofore have been treated with transplantation, which is clearly the favored mode. There aren't very many of them, and I am not sure whether it would make--and I think I stated it--I don't think it would make necessarily much sense in incorporating them, whether we would learn anything different by including them in combined studies. I think we have learned enough or we are learning from the adult experience. We don't have evidence of biological differences.

DR. PRZEPIORKA: You made a very good statement regarding use of asparaginase in pediatric patients and how it has affected their outcome for ALL, and your table also shows the difference in outcomes for adults in pediatric patients, which one may assume may, in part, be due to the differences in treatment with the children being treated far more aggressively since the adults, especially the older adults, can't tolerate the very difficult therapies.

What would you consider ethically

acceptable when it comes to doing a mandated pediatric study which will, of course, we will have to assume has to start with a Phase I study in a population or in a disease where the adults have a very poor prognosis, but the kids have a much better prognosis? Just from your table, the example is B-cell ALL with hyperdiploidy where the pediatric patients have a 89 percent survival, and the adults 30 to 50 percent survival.

Would you really risk a Phase I study in that subgroup of patients?

DR. POPLACK: Would I risk a Phase I study? I think, sure, there is no question that one ought to do it, until we are 100 percent success rate, then, it is appropriate to do Phase I studies. I think the guiding principle always has to be the concern, obviously benefit, but the concern for toxicity. If there were toxicities identified early on that were particularly concerning for children, I think people would be very, very concerned about going forward aggressively.

But as I understand it, this discussion isn't necessarily mandating that studies be done in kids before adults. We are talking about the need

to do studies in both populations. So, we would still be going forward with Phase I studies first being done in adults and then applied to kids.

You are talking about the reverse situation, which toxicity would be greater for adults?

DR. PRZEPIORKA: No, if I had a drug which we used in one of the populations or diseases in adults which had a poor prognosis and showed a marginal, but definite benefit, would it be considered ethically acceptable, then, to mandate study of that drug and that disease in pediatric population where the current therapy already gives a much better outcome than in the adult population.

DR. POPLACK: Again, it depends on the toxicity profile from my perspective.

DR. SANTANA: Just a general comment to remind the committee members, whenever you use examples, be careful in the examples that you use for commercially available agents, and that we are not here to give specific advice on the development of those agents, so use them in the context of the general discussion to set forth a principle or a point of discussion.

Yes.

MS. ETTINGER: I just wanted to sort of tie together two things that Sharon and David said, health benefits to children, which I think is something that obviously we are considering. Toxicity does speak to long-term effects, and I think that when we are talking about children, we always have to remember that, and Dr. Head also brought that up, that we really need to consider not only what the short-term toxicity differences are, but that our patient population in pediatrics are going to live and possibly have long-term effects, which intrigued me in terms of what David said, looking at therapy-related malignancies, which may be some area for us to look at.

DR. SANTANA: Charlie.

DR. SCHIFFER: The rituximab example that you brought up, I think is an interesting one and brings to my mind what we are talking about. You know, rituximab targeted a very small--not a small population--but a less than 50 percent of adults, and subsequent studies using this drug in other lymphoma and leukemia subtypes are in progress.

I think most of us believe that, in general, the most important studies done about how to use a drug occur after the drug is approved.

Certainly the drug is available for both pediatric and adult oncologists to utilize in other disorders if it makes biologic sense.

So, there is no difference if you go between adults and children with regard to this drug, but a difference, and I think the critical difference, if I was a pediatric oncologist, would be if I could get the stuff to use early, if it makes sense in my patient population to evaluate a new drug early rather than waiting until the development is far advanced, so I can get my hands on it.

Rituximab, it probably didn't make initial sense to utilize in many of the pediatric B-cell disorders, as you suggest, as initial studies, but might make sense subsequently as it is being tested in non-follicular types of lymphoma in adults.

I think a real issue that it seems to me is most important is when you can get the drug early to study in children, because it makes the most sense to study it initially in children or the disease is the same in adults and children, and you shouldn't have to wait until the studies are completed in adults.

DR. MURPHY: Charlie, I think you have two

aspects to your comment there. One is the early access to new agents, which is for a variety of reasons problematic, and there can be other discussion as to potential benefits or how that could be realized, but I want to go back to the rituximab example, because I was using it just as an illustration of how, if we were to apply the Rule today, how would it be applied.

That is where I certainly had a problem. I am not disputing your fact that while once it is available, you can test it in other things if it seems logical, but the question is would there be a mandate for this, and that is a different question, particularly if you are talking about mandates in B-cell pediatric lymphomas, they are all high grade and you don't have a lot of time to assess this, you don't have a lot of patients to assess it either because, you know, 80, 90 percent of children with high-grade B-cell lymphomas of any stage are cured now.

That was the point I was trying to make. The early part of it is a whole different thing, not restricted only to rituximab for sure.

DR. SANTANA: Sharon, I think somebody in one of the presentations or earlier discussion, I

think said something that I noted down, which I think is also a very good guiding principle in making this decision, is the focus should be on where the need is, not to apply it to everything, because we have limited populations of patients, because we have patients that are now being cured, so it limits what patients potentially could go into the drug development process.

I think that is where we have to give the advice to the regulatory and governmental groups, that we need to tell them where the focus should be based on where the need is, and not just to test it on everything, and it is hard, it is difficult, I appreciate that.

Bob.

DR. ARCECI: I would concur with your comment, Sharon, on the rituximab. I think that one of the things, however, we miss, and it goes I guess to Charlie's pick up on what you said is the use of these drugs early.

Once they are approved, I think, and I would love to hear what other people have to say on this, I think we lose an opportunity to study them properly, because what I think happens, of course, is that many of our pediatric patients end up

getting treated with the drugs off study for indications that it is unbelievable what a drug like rituximab is being used for now, from autoimmune disease to cancer in children with very, very little data-based, evidence-based studies.

So, I think that without the ability to introduce these drugs early in the context of proper clinical trials, we will lose that because it is very difficult to get a patient on a clinical trial, very early clinical trial, once the drug is approved, because there is no incentive. It can be used, and especially with some of the biologics, which have pretty nice toxicity profiles compared to intensive timing, sequential therapy.

So, I think that there is a potential great, great loss unless we pursue that a little bit further.

Another comment was on--I would love to hear what David and Sharon particularly have to say about the models, such as the MRC, where they have linked their pediatric and adult trials in a sequential fashion over the years, and is that a model that we should be considering further in this country, and would that help us with this agenda.

Lastly, I think in terms of what Steven

and then Sharon commented upon in terms of the definition of this Rule, I think, biologically speaking, it is not whether a translocation is present. That is clearly the case, I think as you pointed out, David, just because you have a translocation doesn't mean the protein is being expressed, and there are many examples developmentally where even the same protein in a different developmental context is going to have a different effect on the function of that cell.

So, the other issue is expression of a protein in those cells. We have the issue of CD20, the issue of CD33. These are antigen markers, so maybe we need to think about broadening the intent of that original concept to the purpose of the therapeutic trial, and expression, not just function, because the mere presence of the antigen may be appropriate then to mandate a study in pediatrics if the intent of the therapy is to target that molecule.

So, it doesn't have to have anything to do with the disease. It could be a differentiation bystander, as Sharon pointed out. I think that is very important. Just doing PCR for translocations is clearly not going to be relevant, as well,

because of all these other modifying genes or expressions.

So, I think we need to think maybe a little bit more about your initial--which I understand was clearly an initial way to start the discussion--but it is far more complex than that, and I think it is not unsolvable, but it would be nice to start thinking in our own minds of laying that out.

DR. SANTANA: Go ahead, Sharon.

DR. MURPHY: Since you directed that to David, and I just have one small comment about trial designs, although I know that is going to be the subject of another session, I think your allusion to the MRC model, the British model for the leukemia trials, is interesting, and I would entertain--I mean we already have good examples of where there has been cooperation here in the States in doing trials for adult and pediatric APL, and the same way with, well, perhaps not entirely the same, with the Ph-positive STI 571.

I wouldn't want to see a complete morphing of leukemia trials to all adult and pediatric, because I think we would lose a lot there, but there may be selected subsets for which it makes

sense, and I would include also lymphomas in that.

We have had some discussions, although no action, about working with the adult cooperative groups to study, for instance, the lymphoblastic lymphomas and the Burkitt lymphomas, of which they don't have a real compelling study design to test, and they would just as soon test it on treatment being tested for younger people, and we could do the biology in tandem and collect a lot of good information, and I think that kind of design makes a lot of sense. Again, it will take a lot of coordination to do it.

DR. POPLACK: If I can just also respond, Bob, I think that one of the things we really don't know, we talk about the prognosis being worse in adult patients with, let's say, a disease like ALL, but we also know that therapy can erode and eliminate the impact of many prognostic factors, and there really have been few examples of identical therapy certainly or even similar therapy being given to a cohort of patients that includes adults and pediatrics.

It is perhaps notable that Dana-Farber now and their consortium are putting together a study where they are going to be putting adults and

children with ALL on similar therapy, but I understand as part of the discussions that are going on, the issues of toxicities are playing a very important role. It is not such an easy thing to do, even if one wanted to, to simply jump into doing identical studies.

DR. SANTANA: Malcolm.

DR. SMITH: To comment on the rituximab as an example of the challenges that we face, and how it also links the issue of early access with the Rule, rituximab hasn't been systematically studied in children yet, but it is not because the drug wasn't available to study, it really is the limited numbers of patients with the relevant lymphomas.

So, there will be studies in children in the next year that will be started, but in this case, it is a real challenge how do you study rituximab in children when you have very limited numbers of children who relapse with current therapies, and then what are the questions that you ask once you do study it.

Perhaps others can address that later, diffuse large B-cell, NHL, in a 15-year-old, what question of therapy do you ask if a rituximab question has been addressed in a 40- or 50- or

60-year-old, what can you extrapolate.

So, not to beat on a specific drug, but it does illustrate the challenges that we will face when we begin to address these targeted therapies.

To address Dr. Przepiorka's question about what can you do with the very good risk patients, how do you integrate new therapies there, just my experience in watching the pediatric groups conduct ALL studies for these populations over the past decade, the risks that you take in that population are very limited.

The questions of therapy that you add have minimal risk associated with them compared to what standard therapy is, and so the question that you might ask in a patient population with Ph-positive ALL with a poor prognosis, that would be very different in terms of the risk associated with it compared to the question for a hyperdiploid or TEL-AML-1 population.

Again, that is one of the challenges we face is targeted therapies may become available for those patient populations.

DR. SANTANA: Malcolm, since you are on that theme, how do you see the interaction between the FDA's mandate to sponsors when these issues

come up and what is happening across the street in terms of the NCI/NIH developmental program for pediatric drug development, is there going to be cross-talk between those two, so that the FDA is not requesting that sponsors do studies that aren't possible to do, I mean where is that advice, where is that communication going to be coming from?

DR. SMITH: I think there will have to be that cross-talk, and the reality check of what can be done within the clinical trial systems that are available to test new agents, and so it is a dialogue with the NCI, it is a dialogue with the Children's Oncology Group, and with others.

You can mandate studying five different new targeted therapies for childhood ALL, but if, in reality, only one could be studied in any reasonable length of time, then, you need to step back and have a dialogue to decide which one should go forward.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: While I know that there certainly is a concern for numbers of patients to study in children, I think that we need to think broader than just the U.S.

There are international investigators who

have collaborated for the past three to four years because they realize that there are rare subsets of children with leukemia that we will not ever learn how to study in Europe or in the U.S. unless we work together, and this collaboration has been going on for some time, so I think we can think that if we have a target and we have a drug that has significant promise, that there will be patients available for us to test in an adequate way.

DR. SANTANA: Susan.

DR. WEINER: I wanted to pick up on Malcolm's comments and others about the coordination between the FDA and the NCI. Malcolm had as a primary concern, and Peter Adamson, and others, of course, the question of prioritization of agents, and it is a real issue as to how the Rule will impact on that prioritization and how the prioritization is going to be decided as the pipeline drugs increase in number and the subject populations decrease with higher success rates.

DR. SANTANA: Steve.

DR. HIRSCHFELD: I wanted to personally express my gratitude for the excellent, excellent presentations that we had from our two initial

speakers, and state that other speakers may possibly repeat some of the themes or maybe different, but we want to have an open discussion, and we also recognize that, as Dr. Murphy pointed out, you can keep splitting infinitely and always find differences, but we are looking for practical ways to approach the problem.

Dr. Murphy brought up a few points which I thought bear some mention, and one is the issue of which drugs are going to be studied, is it only blockbusters, and while they may have been the first ones out of the starting gate or attracted the greatest interest, our analysis of the drugs outside of oncology, which have potential application in pediatrics, is that there are essentially no drugs or major drug classes at least which have not either had studies initiated or have had an interest expressed explicitly in studying them, so the program overall seems to be working.

In fact, I was interviewed extensively by the Wall Street Journal who wanted to put a headline on this theme, only blockbusters, and when we went systematically through the various therapeutic areas, again outside of oncology, we could not find a single contrary example.

In terms of the orphan drugs, that is a potential weakness and everyone recognizes it in the application of the Pediatric Rule. We also have the default state the way the Rule is written that we can always grant a waiver if there are too few patients, so we could categorically exclude all of pediatric oncology and to say there are too few patients and we never have to apply the Rule, and that would be the end of that discussion, but we don't have to do that. In fact, we would like to do otherwise.

And why would we want to look as to how we could apply the Rule, and one of the reasons, which Dr. Arceci touched on, and which we have attempted to put the context in both the exclusivity incentives and the Rule, is that we are looking to establish evidence for use.

We think that using these pediatric initiatives in some cases may be an important catalyst to initiate studies which would provide the types of evidence which we would all like to make our decisions on.

DR. SANTANA: Charlie.

DR. SCHIFFER: Just picking up on one of Bob's comments, I don't bemoan the off-label use

perhaps as much as you stated. I mean particularly in adult oncology, there are problems with off-label use, particularly of cytotoxics where drugs get just thrown at people one after the other, and you have to bemoan that outside of a study context, but on the other hand, that is how we learn how to use drugs when they are on the market and you study different doses and schedules and how to intercalate them into different regimens, and that is most of the trials that are eventually done in adult oncology because the original licensing trials tend to be very narrow and focused with a single goal in mind.

Again, particularly with biologics, some cool stuff happens when you try it in autoimmune disease, for example, and it seems to me the nature of discovery is some imaginative people do it in creative ways, make some observations, which then in a more systematic way either get verified or denied, but I don't have perhaps as much concern about that. I think that is, in fact, how we really learn how to use these drugs.

DR. ARCECI: I would certainly agree with the idea of using the drugs in unique ways after they have been approved is how you get creative

usages in the future, and sometimes the original indication is not what it is best used for in the end.

The problem I have is the--and I think we are probably worse at it or better at it in pediatrics, or maybe not--is the anecdotal aspect of doing it off of a study even in the context of a smaller trial, I think detracts from what we are actually going to ultimately learn in these circumstances.

So, use it in autoimmune disease is a great idea, but don't just give it to a patient and let that result be buried in a clinical record that will never resurface because we never know what the denominator is under those circumstances, so there may be a lot of negatives that never get reported, and, of course, the couple kids who do respond do get reported. I think what we do is unbalance it, so, yeah, use it in new ways, but I would suggest studying it and reporting both negative and positives.

Maybe that is one way the Internet will help us in terms of publications. We can afford electrons maybe more than paper.

DR. SANTANA: Dr. Boyett.

DR. BOYETT: Another point that might be coloring the reason we think that adult cancers and childhood cancers are different, historically, most children with cancer have been treated on clinical trials in university settings. Certainly, you cannot say that for adults, and being a statistician, one wonders just how representative are the 2 to 4 percent of adults with cancers that are treated on clinical trials.

Perhaps if we had 90 percent of the adults with cancers treated on clinical trials, we would really have a better picture of how different or how similar these diseases might be.

DR. SANTANA: One last comment.

DR. WAXMAN: I would like to echo what you are saying. I think the need for studying small numbers of patients like you do in pediatrics well brings a great deal of information that in adult oncology and hematology, we just don't get because there too small number of people are on trial.

So, one of the things we should consider is making these drugs available early, even if it is just a couple of patients that you people study, we are going to learn a great deal and help those children at the same time.

So, I don't think we should worry about the numbers. I think we should worry about getting quality information and having the drugs available for that purpose.

DR. SANTANA: Well, it has been a very interesting discussion, and we will continue during the day. We are by schedule supposed to have a 15-minute break, so we will reconvene at 20 after 10:00.

[Recess.]

DR. SANTANA: We are going to start now on the session on myeloid leukemias. We are going to go ahead and get started because I want to stick to the time limits as best as possible.

David Head is going to give us his perspective on myeloid leukemias and differences or similarities between adult and children.

David.

Perspectives on Myeloid Leukemias

David Head, M.D.

DR. HEAD: Thank you, Victor.

My name is David Head. I am the Vice Chairman of Pathology at Vanderbilt. Before that, I was at St. Jude Children's Research Hospital for 10 years, and I have worked for longer than I will

admit in the federal record with the Pediatric Oncology Group, now part of the Children's Oncology Group and the Southwest Oncology Group and Adult Group. I am a pathologist.

First, let me thank the organizers, Dr. Pazdur, Dr. Hirschfeld, Dr. Santana, and Dr. Somers for arranging this session. I am going to give my perspective of AML classification whether pediatric and adult diseases or the same or different. I think the perspective is slightly different than the perspective that Dr. Murphy gave for lymphoid malignancies, and I will address that a little bit.

Dr. Irv Bernstein is participating, I think, by telephone, although he is not hooked up yet, but I am going to show a few slides of Irv's, one, initially this, and then I will show it again at the end.

Dr. Bernstein, can you hear us? We can't hear you except sporadically.

I am going to try and address a historical perspective of our understanding of myeloid diseases and a more current perspective.

[Slide.]

One of our charges is to compare adult and pediatric disease. This is work that Dr. Bernstein

did in Seattle at Fred Hutchinson Cancer Center, developing CMA-676, also known as Mylotarg, which is an anti-CD33 antibody with calicheamicin attached to it, I believe, that is aimed at killing myeloid cells.

The point of this slide is to show that when he looked at colony formation by leukemic marrow cells from adult versus pediatric patients with AML, that the Mylotarg was actually more effective in the pediatric patients at inhibiting colony formation than in adult patients. Well, how can that be?

With this in mind, let me pose the questions that I posed earlier in open discussion, and that is, the general question, do pediatric and adult AML differ, and I think there are multiple levels to ask this question, do the hosts differ, and we have already discussed the hosts actually do differ. Do the treatment goals differ? The treatment goals may differ depending on the disease, how it is treated, how old the patient is, et cetera.

I am not going to address either of those specifically, but I am going to address two other points. One is do the exact diseases differ,

disease defined on a genetic biological basis, not just generic AML, and the second is do the pathogenesis of the diseases differ, and by "pathogenesis," I don't mean how does, for example, 15;17 cause APL, but what causes the 15;17 to occur, not how does monosomy 7 cause AML or MDS, but what causes the monosomy 7 to occur, so pathogenesis at the level of creating whatever the genetic events are that actually caused the disease.

[Slide.]

So, from my perspective, AML is divisible, from my perspective, into two broad groups of disease. There may be more, but we can at least define, I think, two broad groups of disease.

One has an approximately flat incidence throughout life, and I say "approximate" because we don't know exactly because the studies haven't been done.

The other has an exponential curve with progressive age.

The same general sets of disease occur in the entire patient range. This is a different set of curves than what Sharon Murphy showed for lymphomas, but the ratio of the two differs

depending on where you are in the curve. If you are out here, it is all this MDR-AML or 95 percent, and if you are over here, it is 85 percent TDN-AML.

So, what do I mean by these two sets of disease? The block show the agents and its AML for population at risk, per 100,000 population at risk per year.

[Slide.]

Much of this is published and it is in the folder that was distributed. So, these are the general characteristics of these two sets of disease. More common in the elderly versus relatively flat incidence, often has prior MDS, never has prior MDS, myelodysplastic syndrome, MDS. MDS-like cytogenetics, recurring translocations, multilineage dysplasia and background to hematopoietic cells absent, often clonal background hematopoiesis both at diagnosis and complete remission, nonclonal hematopoiesis, generally poor response to chemotherapy, potentially cured with cytotoxic chemotherapy, differences in MDR1 expression, multidrug resistance gene 1 expression, putatively a different cell of origin, a more primitive stem cell versus at least in some cases a more differentiated stem cell, and we have

iatrogenic models of both of these. Alkylating agents, topo II inhibitors.

Now, some of this is surmised from literature, not much of this was done in prospective study. This is an attempt to garner some kind of logical synthesis out of available data.

[Slide.]

This is quite different than the historical approach to AML, embodied in the FAB classification of AML. This was a very useful exercise generated by a working group of morphologists, the French-American-British group in 1976, with the stated reason if this was to allow evaluation of the efficacy of this historical approach, which was not new with them.

This approach began in the year 1900, and that is not an exaggeration. In 1900, Naegli described myelomonocytic leukemia. That is M4. In 1913, Schilling described monoblastic leukemia. So, we have been doing this for 100 years now, this approach.

[Slide.]

This approach is based on the presumption dating back even to the 1850s that we can

characterize malignancies based on how they recapitulate normal cells. This is a hematopoietic tree, and are the cells erythroblasts or megakaryoblasts, myeloblasts, monoblasts, et cetera. So, this is the historical approach to classification.

Is this approach relevant? Well, this was published in 1976. This is the Southwest Oncology Group study, started in 1978, and I think you can see that there aren't any big messages here, it does not discriminate disease subsets that have different response to at least chemotherapy used on this protocol, and this has been repeated over and over and over again in other studies, so it is clinically, substantially an irrelevant approach.

[Slide.]

This is a different Southwest Oncology Group study, the critical study here being 81;24, that used high-dose anthracycline, high-dose daunorubicin, and it showed a remarkably good outcome in one subset of AML, promyelocytic leukemia.

So, this was initially used to endorse the FAB classification, well, gee, it means something because look at this, but I will just point out

that M3--I will come back to this later--but M3 is essentially a morphogenotype, 95 percent of promyelocytic leukemia or FABM3 as a single cytogenetic translocation that appears to be the driving factor in creating this disease.

So what is important, is it the genotype or is it the morphology? I would submit it is the genotype based on further developments, for example, with all-trans-retinoic acid.

[Slide.]

From the standpoint of our mission today, although this is different subsets, this is young patients meaning less than 60, I believe, on this study, who got high-dose anthracycline, and this is other patients, young and old, who got low-dose anthracycline, and whether young or old, they had basically the same treatment response for anthracycline dosage, but the high-dose anthracycline was not given to elderly patients, illustrating it was because of presumed host differences, but this would suggest the disease is probably the same disease even though the host differs.

[Slide.]

So, I mentioned AML cytogenetics, in

particular 15;17 in promyelocytic leukemia, so let's take a minute to look at cytogenetics in AML. This is far from an inclusive list, but it is one illustration point.

There are a series of recurring translocations that have been described in AML. All of these have now been cloned, the genes have been identified. They are at the breakpoints. There is extensive study in multiple labs about how can these transform, are the single events sufficient to transform or are other events needed to transform, and if so, what are the other events in each case. So, there is extensive study going on with this set of diseases from t(6;9) up.

There are correlates if you start with the cytogenetics and move to the right. So, for example, 8;21 usually has M2 morphology in FAB, but it is not always, it may be other morphologies. 9;11 typically has M5, but it may be a lot of others; 15;17 is 95 percent M3, and version 16, about 50 percent M4eo, but I would suggest that that is not the point of the historical classification, it is not, well, if you know something else, you can go this way, it is if you know this, can you go this way and predict

anything.

I suggest you can't predict very much except for this line here, if you have got M2, what does that mean? Well, it is on almost every line, so even though there are some correlates moving right to left, there are a few correlates moving left to right that hold up. So, I think that is a further indictment of the historical approach.

The second point is from 6;9 up, the median age of all of those is in the 30s, which is the median age of the population. They all have approximately flat incidence in childhood and young adults, but they all persist into the elderly at a diminishing percent of total cases, so this has led me to suggest these must have an approximately flat incidence throughout life, and I think what data are available will support that, although we need more data to corroborate that.

As opposed to that, the second set is found mainly in elderly patients. It is not restricted to them, it is found in younger patients also, 5q- being a possible exception, which is rare in pediatric patients, but generally, -7,7q-, trisomy 8, complex cytogenetics, and a whole litany of other things are found in AML throughout life,

but they exhibit this progressive exponential increase in frequency with progressive age.

A second point is there is essentially no correlation between morphology and these.

[Slide.]

This is the age incidence of AML for population at risk. I showed you that. This is the population in the United States just a few years old. There are the baby-boomers, and they have moved over to here somewhere now, but nevertheless, the curve stays about the same, and if you integrate all this, the median age of AML in the United States and Western Europe is in the 60s, I believe it is 63. As the population ages, it is going to predictably move up because the incidence goes up.

The median age of those recurring translocations is in the 30s, which happens to be the median age of the population, as I mentioned earlier, and the median age of something out here, the rest of the cases must be even greater than 63, must be in the 70s or 80s even.

[Slide.]

This is the age incidence of MDS.

[Slide.]

Let me back up again. This disease in the elderly, that is increasing in incidence for population at risk, and is at least half of AML, has the following characteristics - it is resistant to cytotoxic chemotherapy, it tends to have clonal hematopoiesis, it tends to have clonal remissions, the background marrow is overly sensitive to chemotherapy, so the patients have prolonged cytopenias with aggressive chemotherapy. If they get into remission, the remissions are short-lived, tend to be clonal, and the patient relapses with the same disease.

Although that is what I have just described as AML in the elderly, it also has MDS-like cytogenetics, I left that out, monosomy 7 and 5q-, for example. Although I described that story for the elderly, that story is virtually the same in young patients who have monosomy 7, they just occur at lower incidence.

Over here, that group is 95 percent of the disease, over here it is 15 percent of the disease, but the characteristics of the disease are virtually the same. The only way to cure that set of patients right now appears to be an allogeneic transplant, which we luckily can do over here, we